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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,746	03/03/2004	Franz Paul Armbruster	0756-0124P	2900

2292 7590 11/10/2009

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EXAMINER	
HAQ, SHAFIQUL	
ART UNIT	PAPER NUMBER
1641	

NOTIFICATION DATE	DELIVERY MODE
11/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

Office Action Summary	Application No.	Applicant(s)	
	10/790,746	ARMBRUSTER ET AL.	
	Examiner	Art Unit	
	SHAFIQUL HAQ	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,7-9 and 11-15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,7-9 and 11-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of claims

1. Claims 1-4, 7-9 and 11-15 are pending and examined on merits.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

   The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 1-4, 7-9 and 11-15 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for not clearly reciting the active steps for measuring the amount of 25-hydroxy vitamin D and 1α, 25-hydroxy vitamin D in a sample. It is recommended to re-write each steps clearly so that each of the reaction steps in the method steps are clearly defined. Further, claim 1 recites "measuring displacement of vitamin D derivative of formula (I) from vitamin D binding protein by 25-hydroxy-vitamin D or 1α, 25-dihydroxy vitamin D" in lines 3-5. It is unclear from the claim language as to "vitamin D derivative of formula (I)" is used at what step in the method process and the method step is unclear with regard to the step at which sample is added to the reaction mixture.

5. With regard to claim 14, it is unclear how is 25-hydroxy vitamin D is measured in a sample if 25 hydroxy vitamin D is removed before performing the competitive protein binding assay because claim 1 recites "method of

measuring the amount of 25 hydroxy vitamin D and 1α, 25-hydroxy vitamin D", not only 1α, 25-hydroxy vitamin D.

6. Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 provides for the use of antibody that specifically binds 1α, 25-hydroxy vitamin D in the method of claim 1, but since the claim does not set forth any steps for the use of the antibody in the method/process, it is unclear what method/process applicant is intending to encompass for the use of antibody that specifically binds 1α, 25-hydroxy vitamin D. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claim Rejections - 35 USC § 101

7. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 15 is rejected under 35 U.S.C. 101 because the claimed recitation of a use of antibody that specifically binds 1α, 25-hydroxy vitamin D in the method of claim 1, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example Ex parte Dunki, 153 USPQ 678 (Bd.App. 1967) and Clinical Products, Ltd. v. Brenner, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3 and 11-13 are again rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for measuring the amount of separated (isolated) 1α, 25-hydroxy vitamin D metabolite, does not reasonably provide enablement for measuring the amount of 1α, 25-hydroxy vitamin D metabolite in a sample in the presence of 25-hydroxy vitamin D metabolite in the sample (i.e. in the presence of both the metabolites in a sample) without the separation (isolation) of 1α, 25-hydroxy vitamin D metabolite from the sample. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The method as claimed measures both 25-hydroxy vitamin D metabolite and 1α, 25-hydroxy vitamin D metabolite in a sample by competitive protein binding assay using a vitamin D derivative of formula (I) as a competitor. However, in a sample where the 1α, 25-hydroxy vitamin D metabolite is very low (e.g. human serum where 25-hydroxy vitamin D metabolite to 1α, 25-hydroxy vitamin D metabolite is 1000:1; see paragraph 2, page 34 of specification), the displacement of vitamin D derivative of formula (I) from the vitamin D binding protein would be mainly due to 25-hydroxy vitamin D metabolite and thus the displacement cannot be correlated to the amount of 1α, 25-hydroxy

vitamin D metabolite in the serum sample. See second paragraph (page 34) of specification and page 7 of Applicants' argument (10/10/07), which describe separation of 1α, 25-hydroxy vitamin D from sample by column chromatography for subsequent detection of 1α, 25-hydroxy vitamin D by competitive protein binding assay and thus the method as claimed is not enabled for measuring 1α, 25-hydroxy vitamin D metabolite in the presence of 25 hydroxy vitamin D metabolite and 1α, 25-hydroxy vitamin D metabolite in the sample.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. Claims 1-4, 7-8 and 11 are again rejected under 35 U.S.C. 103(a) as being unpatentable over Holick et al. (WO 97/24127).

Holick teaches methods for detecting the presence of vitamin D analogs and their metabolites in a sample using labeled vitamin D compounds (i.e. vitamin D derivative) in the assay method (see field of invention). The vitamin D metabolites includes , 1,25 dihydroxy vitamin D3, 25 hydroxy vitamin D2 etc. (page 1, lines 12-25 and page 5, lines 10-14) The labeled vitamin D derivative of Holick (see compounds B and C of example 2 and 3 of pages 14-15) reads on the compound of the formula of claim 1 when R represents R

a 25-hydroxy side-group of vitamin D2 or of vitamin D3, Y=H, A= functional group coupled via a spacer group, which can be bound by a protein with high affinity (see definition of A in lines 9-16 of specification wherein A can be biotin). Holick discloses a method in which labeled vitamin D derivative is first allowed to bind to a protein capable of binding to the vitamin D derivative and which is attached to a solid support. Sample containing vitamin D metabolite is then added to effect displacement of the labeled compound from said protein and Holick discloses that preferred protein is vitamin D binding protein (DBP) (see pages 11-12). Holick discloses different immunoassay methods (page 10, lines 21-25 and page 12, lines 9-11) and solid phase support including dextran, agarose, polystyrene and microtitration plate (page 11, lines 27-29) and the solid phase can be beads, plates or tubes (page 10, lines 15-16).

Holick discloses displacement of vitamin D derivatives from vitamin D binding protein (i.e. competitive detection) but remain silent about displacement efficiency with the vitamin D derivative. However as described above, the labeled vitamin D derivatives of Holick are very similar or the same as the vitamin D derivatives of formula (I) of instant application and they are expected to show similar properties (e.g. similar displacement properties from vitamin D binding proteins). PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been

established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)(emphasis added).

With regard to Kit of claims 4 and 7-8, Holick discloses that the labeled compounds are ideally suited for the preparation of a kit and the kit may contain labeled vitamin D derivative, vitamin D binding protein and avidin coated beads, plates etc. (page 10, lines 9-20). Holick does not recite standardized quantity of vitamin D derivatives but standardized quantity of components in a kit composition is obvious to one of ordinary skill in the art.

13. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Holick et al. (WO 97/24127) as described above and further in view of DeLuca et al. (US 5,064,770).

See above teaching for Holick et al.

Holick et al disclose kit comprising solid phase (e.g. beads) and vitamin D derivative but differ from the instant application in failing to disclose magnetic microparticle as solid phase.

DeLuca et al. in a binding assay to determine 1, 25-dihydroxy vitamin D receptor disclose using magnetic particle for anchoring binding molecules to the particle.

Since the use of magnetic particle is very common in the field of immunoassay and magnetic particle has been disclosed for detection of vitamin D binding protein (DeLuca et al.), it would be obvious to one of ordinary skill in the art at the time the invention is made to include magnetic

particle in the method of Holick et al. for detection of vitamin D metabolites involving vitamin D binding protein with a reasonable expectation of success.

Double Patenting

14. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

15. Claims 1-4, 7-8 and 11-13 are again rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 of U.S. Patent No. 6,787,660 in view of Holick et al. (WO 97/24127. (Note that the method claims were not restricted out in the parent application i.e. there was not restriction requirement on the method claims in parent application).

Claims 1-5 of US patent discloses 25-OH vitamin D derivatives which reads on the vitamin D derivative of formula (I). See claims 2 and 5, wherein A can be selected from biotin.

The claims of US patent '660 do not teach using the derivatives in competitive immunoassays.

Holick teaches methods for detecting the presence of vitamin D analogs and their metabolites in a sample using labeled vitamin D compounds (i.e. vitamin D derivative) in the assay method (see field of invention). The vitamin D metabolites includes , 1,25 dihydroxy vitamin D3, 25 hydroxy vitamin D2 etc. (page 1, lines 12-25 and page 5, lines 10-14) Holick discloses a method in which labeled vitamin D derivative is first allowed to bind to a protein capable of binding to the vitamin D derivative and which is attached to a solid support. Sample containing vitamin D metabolite is then added to effect displacement of the labeled compound from said protein and Holick discloses that preferred protein is vitamin D binding protein (DBP) (see pages 11-12). Holick discloses different immunoassay methods (page 10, lines 21-25 and page 12, lines 9-11) and solid phase support including dextran, agarose, polystyrene and microtitration plate (page 11, lines 27-29) and the solid phase can be beads, plates or tubes (page 10, lines 15-16).

Therefore, it would be obvious to one of ordinary skill in the art at the time the invention was made to include the 25-OH derivatives of vitamin D in the competitive immunoassay method of Holick with the expectation of optimization and improving the detection sensitivity of 25-OH vitamin D metabolite and 1, 25-dihydroxy vitamin D metabolite in a sample with a reasonable expectation of success.

Holick discloses displacement of vitamin D derivatives from vitamin D binding protein (i.e. competitive detection) but remain silent about displacement efficiency with the vitamin D derivative. However as described above, the labeled vitamin D derivatives of Holick are very similar or the same as the vitamin D derivatives of formula (I) of instant application and they are expected to show similar properties (e.g. similar displacement properties from vitamin D binding proteins). PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977)(emphasis added).

With regard to Kit of claims 4, 7-9 and 13, Holick discloses that the labeled compounds are ideally suited for the preparation of a kit and the kit may contain labeled vitamin D derivative, vitamin D binding protein and avidin coated beads, plates etc. (page 10, lines 9-20). Holick does not recite standardized quantity of vitamin D derivatives but standardized quantity of components in a kit composition is obvious to one of ordinary skill in the art. With regard to length of biotin group and spacing group, the length of spacers and the length of biotin and spacer of at least one of the compounds A-C and D of the reference encompass the length of 0.9 to 1.5 nm of instant application.

Response to Argument

16. Applicant's arguments and amendments filed 8/5/09 have been fully considered but are persuasive to overcome the rejections under 35 USC 112 second paragraph, 35 USC 112 first paragraph and 35 USC 103 (a).

With regard to rejection under 35 USC 112, second paragraph, Applicants argued that the amendments to claims 1 and 4 obviate the rejection.

Applicants' arguments and amendments have been fully considered but are not persuasive because the method steps are still unclear for the reasons as described in the rejection above in item 4 in this office action.

With regard to 35 USC 112, first paragraph rejection, Applicants argued that the amended claims 1 and 4 recite that the amount o 1α,25-dihydroxy vitamin D and 25-hydroxy vitamin D is measured. However, the amendment does exclude measurement of both 1α,25-dihydroxy vitamin D and 25-hydroxy vitamin D in a sample and does not require separation of 25-hydroxy vitamin D from the sample prior to measurement of 1α,25-dihydroxy vitamin D in the sample.

Applicants argued that the compounds of Holick are distinct from vitamin D derivative of formula (I) but did not mention how the structures are distinct. Applicant further argued that Holick's displacement ligands demonstrate a displacement efficiency approximately 1/11 that of the present compounds of formula (I) now claimed.

Applicants' arguments have been fully considered but are not persuasive because labeled vitamin D derivatives of Holick are a structural homolog of

vitamin D derivatives of formula (I) of instant application. As for example, compare the compound c (page 15 of the reference) with formula (I). Considering Y=H, and R=25 hydroxylated side-group of vitamin D, the only difference lies in the alkylene chain in the linker (four CH_2 groups versus five CH_2 groups in between two amide bonds). Therefore, the compound of the reference is a chain homolog of the compound of instant application (differ by only one methylene group) and they are expected to show similar properties {e.g. similar displacement properties at that of formula (I)}. PRODUCT, MPEP §2112 states "[Where] the claimed and prior art products are identical or substantially identical in structure or composition, or are produced by identical or substantially identical processes, a prima facie case of either anticipation or obviousness has been established." In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433 (CCPA 1977) (emphasis added). Further, homologs (compounds differing regularly by the successive addition of the same chemical group, e.g., by -CH_2- groups) are generally of sufficiently close structural similarity that there is a presumed expectation that such compounds possess similar properties. In re Wilder, 563 F.2d 457, 195 USPQ 426 (CCPA 1977). Since the compound of formula (I) and the compound c of the reference is a chain homolog (differ by only one CH_2 group in the linker), the Examiner maintains that they would exhibit similar displacement properties in a same experimental setup for measurement of displacement efficiency in the absence of any unobviousness or unexpected properties.

"Displacement efficiency" and the method to measure the displacement efficiency has not been clearly defined in the specification and Applicants have not shown different properties (i.e. different displacement properties) of the compound of formula **(I)** from the compound disclosed by Holick (e.g. compound c of page 15 which is in question) in a same experimental setup (i.e. using the same method process) for measurement of displacement properties. The measurement of displacement for the compound of formula (I) of instant application and the method used in the reference for measuring efficiency of displacement may not be the same and Applicants cannot draw a conclusion form this and assert that they have different displacement efficiency.

Conclusion

17. Applicants' amendment necessitated new ground(s) of rejection presented in this office action. Accordingly, **THIS ACTION IS MADE FINAL**. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action.

In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

If Applicants should amend the claims, a complete and responsive reply will clearly identify where support can be found in the disclosure for each amendment. Applicant should point to the page and line numbers of the application corresponding to each amendment, and provide any statements that might help to identify support for the claimed invention (e.g., if the amendment is not supported in ipsis verbis, clarification on the record may be helpful). Should Applicants present new claims, Applicants should clearly identify where support can be found in the disclosure.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shafiqul Haq whose telephone number is 571-272-6103. The examiner can normally be reached on 7:30AM-4:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark L. Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Shafiqul Haq/
Primary Examiner, Art Unit 1641